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Individual Thermogenic Responses to Mild Cold and Overfeeding Are Closely Related

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Context: Adaptive thermogenesis is defined as the increase in energy expenditure in response to overfeeding or cold. Large interindividual differences in adaptive thermogenesis have been described.

Objective: Because there are indications for a common underlying mechanism, we studied in humans whether the increase in thermogenesis during short-term overfeeding (3 d) is related to mild cold-induced thermogenesis.

Interventions: Thirteen lean male subjects have been exposed to three experimental conditions in respiration chambers: baseline (36 h in energy balance at thermoneutrality, 22 C), overfeeding (84 h at 160% of energy balance, 22 C), and mild cold (84 h in energy balance, 16 C).

Main Outcome Measures: During the interventions, total daily energy expenditure (TDEE), physical activity, skin temperatures, and core temperature were measured. After each condition, fasting plasma norepinephrine concentration was measured.

Results: Overfeeding caused significant increases in TDEE (0.77 MJ/d, $P < 0.001$). During cold exposure TDEE increased significantly (0.59 MJ/d, $P < 0.005$), whereas physical activity decreased. The changes in TDEE during both overfeeding and mild cold exposure showed considerable interindividual variation (respectively, −0.11 to 1.61 MJ/d and −0.19 to 1.58 MJ/d). The individual changes in energy expenditure during mild cold exposure and overfeeding were highly correlated ($P < 0.005$). Fasting norepinephrine plasma concentrations correlated significantly to energy expenditure in both situations ($P < 0.05$).

Conclusions: These results suggest that both overfeeding-induced and mild cold-induced adaptive thermogenesis share common regulating mechanisms. This indicates that cold exposure could be used as a biomarker for the individual thermogenic response to excess energy intake. **(*J Clin Endocrinol Metab* 92: 4299–4305, 2007)**

IN RECENT YEARS, the prevalence of obesity has been increasing in both developed and developing countries (1). Obesity develops when energy intake exceeds energy expenditure. However, after overfeeding, the same amount of excess energy intake does not invoke the same body weight gain in all people. Bouchard *et al.* (2) showed a range in weight gain of 4.3–13.3 kg after an excess energy intake of 353 MJ in 100 d. This implies large individual differences with a 3-fold range in energy cost of weight gain from 27–82 MJ/kg. These observations were confirmed by others (3, 4).

Because energy intake was standardized in the abovementioned studies, the differences in weight gain have to be caused by a difference in energy expenditure. The most variable parts are activity-induced energy expenditure and diet-induced thermogenesis (DIT). Part of the interindividual differences may be explained by an increase in activity-induced energy expenditure. However, DIT will also be affected. DIT can be divided into two categories: obligatory and facultative DIT. The obligatory part of DIT consists of all processes related to digestion, absorption, and processing of food. The facultative component enables dissipating of energy as heat after a high-calorie meal and prevents the storage of energy. Part of the interindividual differences in weight gain can be explained by the variability in potency of this facultative component (5). After reanalysis of several human studies, Stock (6) showed that considerable interindividual differences exist in facultative thermogenesis.

Similar to excess energy intake, large interindividual differences in energy expenditure have been found when subjects are exposed to mild cold. After a 24-h exposure to 16 C (with a baseline at 22 C), the total daily energy expenditure (TDEE) increases with 0.8 MJ/d; however, the range in interindividual variation was between 0.15 and 1.45 MJ/d (7). Similar results have been found after a decrease in chamber temperature from 28 to 22 C (8).

Adaptive thermogenesis protects the body from cold exposure or regulates energy balance after changes in diet. Possible mechanisms in both humans and small mammals are mitochondrial uncoupling, protein turnover, futile cycling, and nonexercise activity thermogenesis (NEAT) (3, 9). With respect to the regulation, it is clear that the sympathetic nervous system plays an important role in these processes. Animal studies show that blocking of the sympathetic nervous system, which innervates brown adipose tissue and skeletal muscle, impairs temperature regulation during cold exposure and increases storage of calories during normal caloric intake (9). In humans, it is known that both overfeeding and cold exposure lead to an increase in sympathetic activity (10, 11). Moreover, it has been shown that epinephrine infusion in the forearm increased energy expenditure for

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Abbreviations: DIT, Diet-induced thermogenesis; FFA, free fatty acids; FFM, fat-free mass; NEAT, nonexercise activity thermogenesis; PAI, physical activity index; RQ, respiratory quotient; SMR, sleeping metabolic rate; TDEE, total daily energy expenditure; UCP, uncoupling protein.

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TABLE 1. Subject characteristics

	Mean	SEM
Age (yr)	22.77	1.72
Height (m)	1.86	0.03
Weight (kg)	79.63	3.97
Body mass index (kg/m^2)	22.96	0.90
Body fat (%)	16.66	1.55
FFM (kg)	65.84	2.45

more than 15% (12). The fact that both overfeeding-induced and cold-induced adaptive thermogenesis are regulated by the sympathetic nervous system gives rise to the assumption that both forms of adaptive thermogenesis share the same mechanisms. Accordingly, we hypothesized that the individual increases in energy expenditure during short-term overfeeding and mild cold exposure are related. For that purpose, the major metabolic routes of energy expenditure were compared between 3 d of overfeeding and 3 d of mild cold exposure in 13 male subjects.

Subjects and Methods

Thirteen healthy male Caucasian volunteers participated in this study. Subject characteristics are shown in Table 1. All subjects signed an informed consent for the study protocol, which was approved by the Institutional Review Board of Maastricht University.

Experimental protocol

Subjects stayed three times in a respiration chamber (13), twice for 36 h and once for 84 h (Fig. 1). In both 36-h situations, room temperature was 22 C. During one stay, subjects were fed in energy balance (baseline), and during the other stay, they received a high-energy diet during the stay and 48 h before entering the chamber (overfeeding). In the 84-h situation, the room temperature was 16 C and subjects were fed in energy balance (mild cold). After the baseline situation, subjects were randomly assigned to both other situations. The temperature of the mild cold situation (16 C) in this study setting had been validated earlier (14). No shivering occurred in that previous study (14), as was verified with electromyography. Nevertheless, in the present study, each participant had to fill out an hourly questionnaire about whether shivering occurred. Energy balance was based on individually calculated energy requirements; after measurement of sleeping metabolic rate (SMR) during the first night in the respiration chamber, an estimated TDEE was calculated by multiplying SMR with a physical activity index (PAI) of 1.6 (15). Energy intake was adjusted accordingly.

During overfeeding, subjects received a diet containing 160% of the energy required for energy balance 2 d before and during their stay in the respiration chamber. The PAI of the free-living situation was estimated after questioning the subject; for each hour of moderate physical activity per day, the PAI was increased with 0.2 above the standard 1.6 for sedentary subjects. The SMR of the previous respiration chamber stay was used as a base for this calculation.

Macronutrient composition of all meals was 47, 38, and 15% energy from carbohydrate, fat, and protein, respectively.

Subjects entered the respiration chamber at 2000 h. The first night they could become accustomed to to the situation. Clothing was standardized. A standard daily activity protocol was applied (16), which described all activities required by the subjects. The subjects measured their own body weight each morning in fasted state after voiding on a digital balance, accurate to the nearest 0.1 kg.

Immediately upon leaving the respiration chamber, blood samples were drawn from an iv catheter that was inserted 30 min earlier. The interval between two stays in the chamber was at least 2 wk.

Energy expenditure

The respiration chamber is a 14-m^3 room, furnished with a bed, chair, television, radio, telephone, computer, washbowl, and deep-freeze toilet. Air locks provide passage for exchange of food and urine. Energy expenditure was determined from the subjects' O_2 consumption, CO_2 production, and urine nitrogen excretion according to the Weir equation (17). The respiration chamber was ventilated with fresh air at a rate of 70–80 liters/min. A dry gas meter (G4; Schlumberger, Dordrecht The Netherlands) measured the ventilation rate. A paramagnetic O_2 analyzer (OA 184A; Servomex, Crowborough, UK) and an infrared CO_2 analyzer (Uras 3G; Hartmann & Braun, Frankfurt am Main, Germany) were used to analyze the samples of the in- and outgoing air. Ingoing air was analyzed once every 15 min and outgoing air every 5 min. Relative humidity was kept between 53 and 55%. Physical activity was monitored by means of a radar system, based on the Doppler principle (13). Twenty-four-hour urine samples were collected in containers with 10 ml H_2SO_4 to prevent nitrogen loss by evaporation. Total daily nitrogen excretion was calculated with 24-h urine nitrogen concentration, which was measured with a nitrogen analyzer (CHN-O-Rapid; Heraeus, Hanau, Germany).

TDEE was calculated over 24-h intervals from 0800–0800 h. SMR is defined to be the lowest energy expenditure at night (measured over three consecutive hours). Both TDEE and SMR have been corrected for fat-free mass (FFM) through linear regression, because 80% of interindividual differences in energy expenditure can be explained by FFM (18). The residuals of the regression between energy expenditure and FFM have been added to the average energy expenditure.

Body temperature

Skin temperatures were measured continuously during the experiments by means of iButtons (type DS1921H; Maxim/Dallas Semiconductor Corp., Dallas, TX), which have recently been validated for studies in humans (20). Temperature sensors were attached to the skin using fixomull tape (BSN, Hamburg, Germany) at the 15 positions of the adapted Mitchell/Wyndham equation for mean skin temperature (21). The averages of temperatures of the face, chest, abdomen, scapula, subscapula, and lower back were regarded as proximal temperatures.

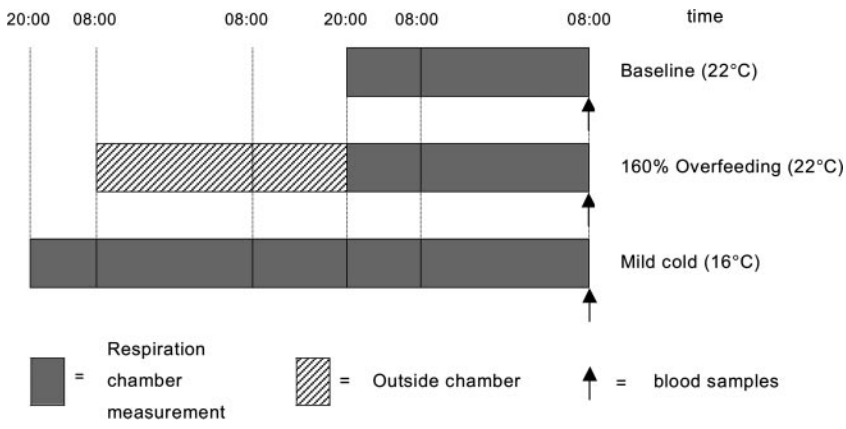

FIG. 1. The experimental procedure followed by each subject. Each subject followed all three situations, starting with the baseline measurement. Baseline and overfeeding measurements comprised 36 h in the respiration chamber, mild cold measurements 84 h. After each stay, blood samples were taken.

TABLE 2. Summarized respiration chamber data

	Mean ± SEM			ANOVA, *P*	Overfeeding – baseline		Cold – baseline	
	Baseline	Overfeeding	Cold		δ	*P*	δ	*P*
TDEE corrected for FFM (MJ/d)	11.47 ± 0.11	12.23 ± 0.17	12.06 ± 0.17	<0.001	0.77	<0.001	0.59	0.003
SMR corrected for FFM (MJ/d)	7.51 ± 0.09	7.98 ± 0.12	7.52 ± 0.09	<0.001	0.47	0.001	0.015	0.84
Activity (kcounts/d)	0.21 ± 0.01	0.22 ± 0.01	0.17 ± 0.01	<0.001	0.0092	0.44	−0.039	<0.001
RQ	0.87 ± 0.01	0.93 ± 0.01	0.87 ± 0.01	<0.001	0.057	<0.001	−0.00077	0.94
Urine nitrogen (g/d)	13.86 ± 0.50	17.96 ± 0.67	13.92 ± 0.57	<0.001	4.1	<0.001	0.063	0.92

Averages of hand and foot temperatures were regarded as distal temperatures. Core temperatures were measured the last 24 h of each respiration chamber stay using a telemetric pill (CorTemp; HQInc, Palmetto, FL) that measures temperature in the intestine and transmits data to a mobile receiver. The silicon-coated pill was ingested with breakfast.

Body composition

Whole-body density was determined in the fasted state by hydrodensitometry with simultaneous assessment of the lung volume using the helium dilution technique. Body weight was measured using a digital balance with an accuracy of 0.001 kg (ID1 plus; Mettler Toledo, Tiel, The Netherlands). Under water, body weight was measured using a digital balance with an accuracy of 0.01 kg (E1200; Sauter, Ebingen,Germany). Lung volume was measured by use of a spirometer (Volugraph 2000; Mijnhardt, Bunnik, The Netherlands). Percent body fat was calculated using the equation of Siri (22).

Blood analyses

Blood samples in the fasted state were taken to assess catecholamine, insulin, leptin, free fatty acids (FFA), adiponectin, and active ghrelin levels. Catecholamine blood samples were taken in lithium-heparin-containing tubes. Other samples were taken in EDTA-containing tubes to prevent clotting. Plasma was obtained by centrifugation, frozen in liquid nitrogen, and stored at −80 C until further analysis. Before centrifugation, glutathione was added to the catecholamine samples and phenylmethylsulfonyl fluoride was added to the active ghrelin samples. Plasma insulin, leptin, FFA, active ghrelin, and adiponectin levels were determined using RIA (Linco Research, St. Charles, MO). Catecholamine levels were assessed by HPLC according to the method of Alberts *et al.* (23).

Statistics

Comparisons were made using ANOVA repeated measures, with simple contrast for individual comparisons between groups. Linear regression analyses were made to identify correlations between cold- and overfeeding-induced changes and between variables. Cook's distances larger than 0.5 and studentized deleted residuals larger than 4.0 were considered to be outliers. Statistical analyses were performed using SPSS 11.0 for Mac. Values were considered to be statistically significant if $P < 0.05$.

Results

Energy expenditure

TDEE (corrected for FFM) increased significantly during both overfeeding ($P < 0.001$) and mild cold exposure ($P < 0.005$) (Table 2). Overfeeding caused an average increase of 0.76 MJ/d (6.6% of TDEE), with a range of −0.11 to 1.61 MJ/d (0–14%). During mild cold exposure, an increase of 0.59 MJ/d (5.1% of TDEE) occurred, with a range of −0.19 to 1.58 MJ/d (0–14%). The increase in TDEE during overfeeding was significantly related to the increase in TDEE during mild cold exposure (r = 0.63; $P < 0.05$) (*dotted line*, Fig. 2A). After deleting an outlier (subject 11, Cook's distance 0.75) the regression improved substantially (r = 0.75; $P < 0.005$) (*solid line*, Fig. 2A). SMR (corrected for FFM) increased significantly during overfeeding only ($P < 0.005$), not during mild cold exposure (Table 2). The change in SMR during overfeeding correlated significantly to the change during mild cold ex-

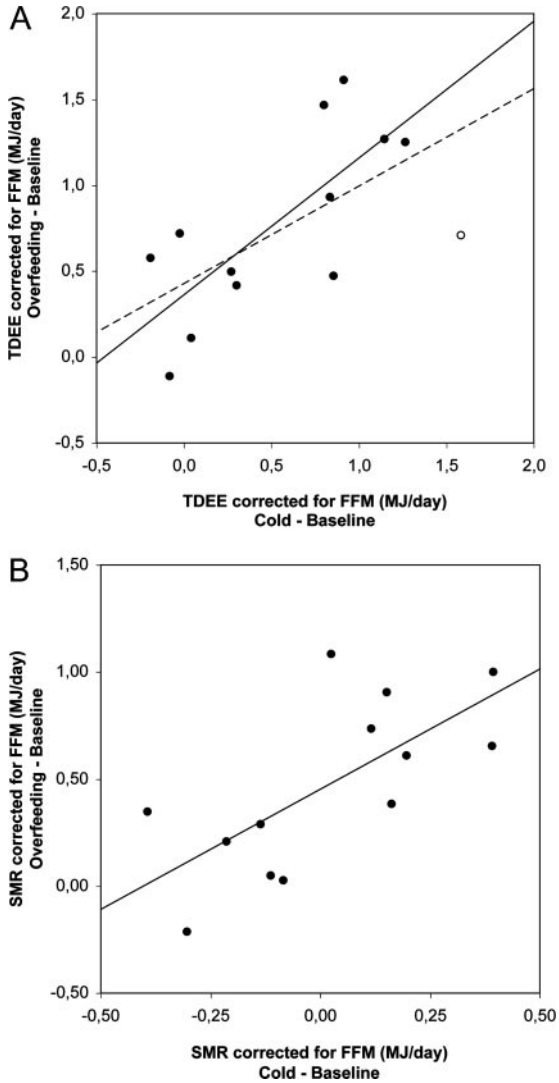

FIG. 2. Energy expenditure: overfeeding *vs.* mild cold exposure. The relations between the change in TDEE (A) and SMR (B) corrected for FFM during overfeeding and during mild cold exposure. The correlation coefficient of this relation for TDEE was 0.63 ($P < 0.05$). One outlier (Cook's distance 0.75) existed; reviewing questionnaire data revealed that the subject was more stressed in the mild cold situation than in both the baseline and the overfeeding situation. Stress could increase energy expenditure, and therefore this subject was excluded from this analysis. The correlation coefficient after removing was 0.75 ($P < 0.005$). The correlation coefficient of this relation for SMR was 0.69 ($P < 0.01$). No outliers existed.

TABLE 3. Summarized temperature data

	Mean ± SEM			ANOVA, *P*	Overfeeding – baseline		Cold – baseline	
	Baseline	Overfeeding	Cold		δ	*P*	δ	*P*
Core temperature (C)	36.93 ± 0.08	37.10 ± 0.06	37.04 ± 0.05	0.10	0.17	0.035	0.11	0.20
Skin temperature (C)	32.82 ± 0.15	33.12 ± 0.16	30.42 ± 0.19	<0.001	0.30	0.030	−2.4	<0.001
Proximal skin temperature (C)	33.48 ± 0.17	33.80 ± 0.18	31.94 ± 0.27	<0.001	0.32	0.026	−1.5	<0.001
Distal skin temperature (C)	31.89 ± 0.28	32.44 ± 0.25	26.42 ± 0.52	<0.001	0.55	0.024	−5.5	<0.001
Gradient core-proximal skin temperature (C)	3.46 ± 0.17	3.35 ± 0.18	5.32 ± 0.29	<0.001	−0.11	0.44	1.9	<0.001
Gradient proximal-distal skin temperature (C)	1.59 ± 0.31	1.36 ± 0.29	5.52 ± 0.66	<0.001	0.23	0.25	3.9	<0.001

posure (r = 0.69; $P < 0.01$) (Fig. 2B). Respiratory quotient (RQ) and urine nitrogen production increased significantly during overfeeding (both $P < 0.001$). Activity counts decreased significantly during cold exposure ($P < 0.001$).

Body temperature

During overfeeding, core temperature, skin temperature, proximal skin temperature, and distal skin temperature increased ($P < 0.05$) (Table 3). During mild cold exposure, core temperature was not significantly different, but skin temperature, proximal skin temperature, and distal skin temperature decreased significantly ($P < 0.001$) (Table 3). The gradients core-proximal and proximal-distal temperature, measures for core insulation, increased significantly during mild cold exposure (both $P < 0.001$) (Table 3). Changes in core and skin temperatures during overfeeding and mild cold exposure did not correlate. Energy expenditure did not correlate significantly with core temperature, skin temperatures, or temperature gradients.

Blood analyses

Fasting insulin, norepinephrine, epinephrine, active ghrelin, and adiponectin concentration did not change after overfeeding. However, the overfeeding experiment did result in a significant decrease in fasting FFA concentration ($P < 0.005$) and an increase in leptin concentration ($P < 0.05$) (Table 4). After mild cold exposure, only fasting norepinephrine concentration increased significantly ($P < 0.001$). No significant changes in the plasma concentration of fasting insulin, epinephrine, FFA, leptin, active ghrelin, and adiponectin occurred (Table 4). Changes in fasting insulin, norepinephrine, FFA, active ghrelin, and adiponectin concentrations after overfeeding correlated with the changes after mild cold exposure [respectively, r = 0.84, $P < 0.001$; r = 0.87, $P < 0.002$ (with outlier correction); r = 0.92, $P < 0.001$ (with correction for Cook's distance); r = 0.78, $P < 0.05$; and r = 0.57, $P = 0.051$]. Changes in leptin plasma concentration after overfeeding and mild cold exposure did not correlate. Leptin concentrations correlated with body fat (r = 0.83, $P < 0.002$; r = 0.84, $P < 0.001$; and r = 0.92, $P < 0.001$ for baseline, overfeeding, and mild cold exposure, respectively). Remarkably, the change in leptin concentration after overfeeding correlated also to body fat (r = 0.77, $P < 0.005$). Differences in energy expenditure correlated significantly to differences in fasting plasma norepinephrine level after both overfeeding (r = 0.56, $P < 0.05$) and mild cold exposure (r = 0.72, $P < 0.02$) (Fig. 3), although no significant change in norepinephrine after overfeeding exists.

Discussion

We hypothesized that the individual responses in energy expenditure during mild cold exposure and during short-time overfeeding are related. The results showed that there are indeed significant relations.

Overfeeding caused an increase in energy expenditure of 0.71 MJ/d, which is 6.7% of the TDEE. The range is large, −0.11 to 1.61 MJ/d (0–14%). Some subjects dissipated none of the extra energy ingested, whereas others dissipated up to 23% of this excess. This difference can lead to a considerable variation in weight gain after overfeeding and might therefore be a factor in the development of obesity. The large variation in weight gain has been shown by several groups (2–4). Our results show similar interindividual differences in energy expenditure.

Mild cold exposure caused an increase in energy expenditure of 0.59 MJ/d (5.1% of TDEE) with a similar range of −0.19 to 1.58 MJ/d (0–14%). This is consistent to earlier studies (7, 8) and comparable to the change in energy expenditure after overfeeding. It is for the first time demonstrated that the individual responses to overfeeding and cold exposure are so closely related to each other.

The mechanism behind these increases in energy expenditure are often attributed to an increase of physical activity or to NEAT (3, 24). However, the radar activity counts decreased during overfeeding and mild cold exposure. Therefore, it is unlikely that NEAT contributed to the increases in energy expenditure.

SMR was not changed during mild cold exposure, because subjects could create their own microclimate under the duvet at night. However, SMR change during mild cold exposure correlated to the change during overfeeding. This can be explained by a prolonged action of the increase in energy expenditure during mild cold exposure in the metabolic responders during night. Another possibility is a metabolic reaction due to the low face temperature, which can act as a cold sensor (25). SMR was increased during overfeeding, indicating that the DIT lasted for many hours after the last meal. This has been observed before (4, 26). Consequently, it is likely that we did not measure a SMR, but SMR plus a part of the DIT.

The increased RQ and nitrogen production and the decrease of fasted plasma FFA concentration in the overfeeding situation can be explained by a quantitatively larger amount of proteins and carbohydrates in the diet consumed relative to fat (27). The amount of fat not expended is most probably stored in the adipose tissue and to a lesser extent in muscle.

In line with the increase in energy expenditure, the in-

TABLE 4. Summarized blood sample data

	Mean ± SEM			ANOVA, *P*	Overfeeding–baseline		Cold– baseline	
	Baseline	Overfeeding	Cold		δ	*P*	δ	*P*
Insulin (μU/ml)	14.13 ± 1.34	15.07 ± 0.92	12.71 ± 0.89	0.13	0.94	0.40	−1.4	0.34
Norepinephrine (ng/liter)	376.5 ± 37.4	359.9 ± 38.9	646.1 ± 57.9	<0.001	−16.6	0.74	269.6	<0.001
Epinephrine (ng/liter)	40.29 ± 3.71	39.62 ± 5.43	33.05 ± 3.11	0.36	−0.66	0.91	−7.24	0.074
FFA (pmol/ml)	290.1 ± 24.7	163.7 ± 13.0	301.2 ± 37.2	0.001	−126.3	0.001	11.2	0.74
Leptin (ng/ml)	3.99 ± 0.81	4.83 ± 1.00	3.67 ± 0.63	0.039	0.85	0.048	−0.32	0.49
Active ghrelin (pg/ml)	42.74 ± 2.80	40.00 ± 4.05	51.98 ± 6.11	0.11	−2.7	0.55	9.2	0.24
Adiponectin (ng/ml)	8.96 ± 1.12	9.25 ± 0.90	9.04 ± 1.02	0.87	0.29	0.62	0.072	0.90

creases of skin temperatures relative to baseline during overfeeding indicate extra dissipation of heat to the environment. To our knowledge, no other overfeeding studies registered skin temperatures. An increase in skin temperature has been shown directly after a large meal (28). The elevation in core temperature shows up in the results of Rising *et al.* (29), who showed that after starvation, core temperature dropped and increased again after refeeding. During cold exposure, however, skin temperature decreased, with a concomitant rise in energy expenditure. This is caused by the large heat loss to the environment, which cannot be measured using temperature probes only. Because temperature gradients between environment and body were different for overfeeding and mild cold exposure, no correlations could be found between the differences in skin and core temperature. To assess these relations, heat flux measurements are needed.

Leptin is widely recognized as a regulator of adipose tissue mass. A high level of leptin is associated with a large adipose tissue mass and signals for positive energy balance. A low level of leptin works the other way around (30). Our study confirms that leptin concentration is correlated to fat mass. Indeed, in obese subjects, leptin levels are elevated. However, in obese subjects, energy balance is often not changed due to an increased insensitivity to leptin (30).

Although leptin is generally accepted to be a long-term regulator of energy balance, less well known is our observation that plasma leptin concentration increased after short-term overfeeding. This indicates a fast response of leptin upon activation of adipose tissue to prevent excess energy storage (31). Moreover, our study shows that the increase in leptin concentration is also related to body fat. This can be explained by the larger secreting tissue (*i.e.* the adipose tissue).

Overfeeding and mild cold exposure shared 57% of their interindividual variation in total daily energy expenditure. This indicates that both cold- and overfeeding-induced adaptive thermogenesis share the same regulation. This common origin has previously been shown in several studies in mice, as reviewed by Lowell and Spiegelman (9). It has been shown that the sympathetic nervous system regulates adaptive thermogenesis in animals (32, 33). Also in humans, sympathetic stimulation of skeletal muscle results in an increase in energy expenditure (12). Therefore, it is likely that interindividual differences in sensitivity or activity of the sympathetic nervous system are responsible for the large interindividual differences in adaptive thermogenesis. The correlations of changes in fasting norepinephrine plasma levels with changes in TDEE after both overfeeding and mild cold exposure indicate that a larger secretion of norepinephrine causes increases in energy expenditure. Correlations of the changes of fasting plasma insulin, adiponectin, active ghrelin, and FFA after overfeeding and mild cold exposure underline the role of the sympathetic nervous system in adaptive thermogenesis. Several recent studies indicate the central role of the sympathetic nervous system in the regulation of these parameters. First, epinephrine is able to inhibit

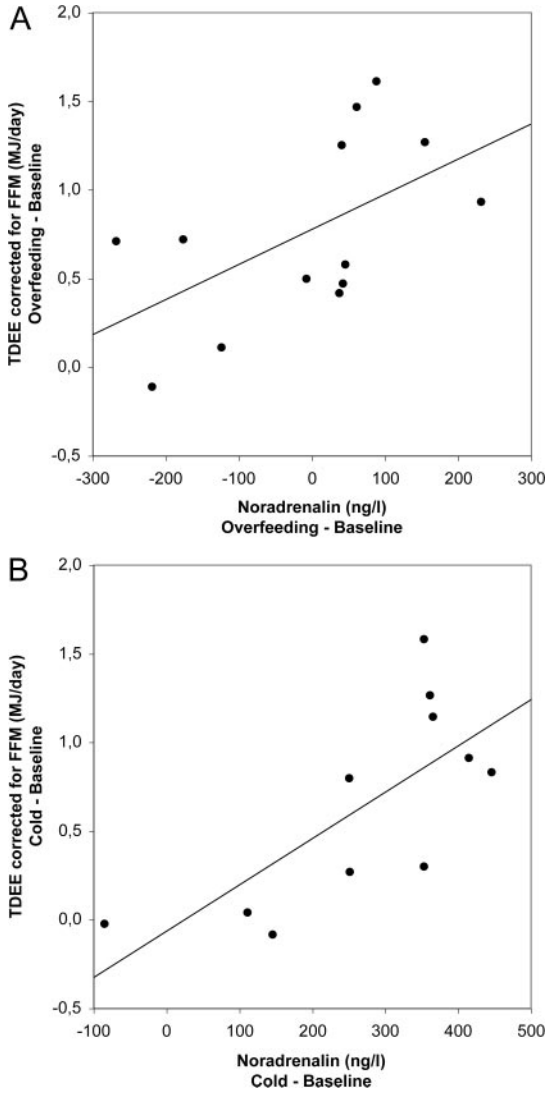

FIG. 3. TDEE *vs.* norepinephrine concentrations. The relation between the change in TDEE corrected for FFM and fasting plasma norepinephrine concentration during both overfeeding ($r = 0.56$, $P < 0.05$) (A) and mild cold exposure ($r = 0.72$, $P < 0.02$) (B).

pancreatic insulin secretion (34); hence, fasting plasma insulin levels might be decreased in sympathetic responders. Second, blocking the sympathetic nervous system increases adiponectin plasma levels (35). Third, electrical stimulation of the sympathetic nervous system invoked an increase in ghrelin concentration in rats (36). Fourth, administration of β-adrenergic agonists stimulate lipolysis, which increases FFA concentrations (37, 38). Therefore, there are strong indications that the sympathetic nervous system is the main regulator of adaptive thermogenesis.

In small mammals, brown adipose tissue serves as a thermogenic organ, which uncouples mitochondrial respiration using an uncoupling protein (UCP)-1. UCP-1 activity is regulated by the β-cells of the sympathetic nervous system. The relevance of brown adipose tissue is believed to be marginal in most adult humans (39), although recent data indicate cold-induced activity of brown adipose tissue in adults (40). Another potential mechanism in humans is uncoupling by UCP-3, a UCP-1 homolog that is present in skeletal muscle tissue. However, it has been shown that the UCP-3 protein content and mRNA expression have not been increased after mild cold exposure (41). On the other hand, FFA are known to stimulate UCP-3 activity (42). High metabolic responders show a less decreased FFA concentration than low responders after overfeeding. After mild cold exposure, high metabolic responders even show an increase in FFA concentration. This (relative) increase in FFA concentration in high responders might cause an increased mitochondrial uncoupling in skeletal muscle compared with low responders, possibly through UCP-3.

The relation in the metabolic reaction to overfeeding and mild cold exposure is not only helpful in the identification of the underlying mechanisms. Mild cold exposure *per se* might also work as a prevention method or cure for obesity, because it is easy to decrease home temperature slightly (19). However, it is not entirely possible to translate our results directly to other groups such as obese subjects or women, because of possible different metabolic responses. Therefore, these groups will be studied in the near future.

We initiated this study to see whether cold exposure could be used as a proxy functional test for the individual thermogenic capacity in a situation of excess energy intake. Overfeeding is a complex and tedious type of functional test and not very appreciated by subjects, in particular obese subjects. The results do show an excellent correlation and could lead to a simpler functional test for thermogenic capacity.

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Erratum

In the article "11p15 Imprinting Center Region 1 Loss of Methylation Is a Common and Specific Cause of Typical Russell-Silver Syndrome: Clinical Scoring System and Epigenetic-Phenotypic Correlations" by Irène Netchine, Sylvie Rossignol, Marie-Noëlle Dufourg, Salah Azzi, Alexandra Rousseau, Laurence Perin, Muriel Houang, Virginie Steunou, Blandine Esteva, Nathalie Thibaud, Marie-Charles Raux Demay, Fabienne Danton, Elzbieta Petriczko, Anne-Marie Bertrand, Claudine Heinrichs, Jean-Claude Carel, Guy-André Loeuille, Graziella Pinto, Marie-Line Jacquemont, Christine Gicquel, Sylvie Cabrol, and Yves Le Bouc (*The Journal of Clinical Endocrinology & Metabolism* **92:**3148–3154, 2007), the printer mistakenly identified the paper as a Brief Report. It is actually a Full-Length Original Article in the Endocrine Care section. *The printer apologizes for their error.*